Equivariant 3D-conditional diffusion model for molecular linker design

Year: 2022 | Citations: 212 | Authors: Ilia Igashov, Hannes Stärk, Clément Vignac, Arne Schneuing, Victor Garcia Satorras

---

Abstract

Fragment-based drug discovery has been an effective paradigm in early-stage drug development. An open challenge in this area is designing linkers between disconnected molecular fragments of interest to obtain chemically relevant candidate drug molecules. In this work, we propose DiffLinker, an E(3)-equivariant three-dimensional conditional diffusion model for molecular linker design. Given a set of disconnected fragments, our model places missing atoms in between and designs a molecule incorporating all the initial fragments. Unlike previous approaches that are only able to connect pairs of molecular fragments, our method can link an arbitrary number of fragments. Additionally, the model automatically determines the number of atoms in the linker and its attachment points to the input fragments. We demonstrate that DiffLinker outperforms other methods on the standard datasets, generating more diverse and synthetically accessible molecules. We experimentally test our method in real-world applications, showing that it can successfully generate valid linkers conditioned on target protein pockets. Fragment-based molecular design uses chemical motifs and combines them into bio-active compounds. While this approach has grown in capability, molecular linker methods are restricted to linking fragments one by one, which makes the search for effective combinations harder. Igashov and colleagues use a conditional diffusion model to link multiple fragments in a one-shot generative process.